APPENDIX A

ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Refractory Ceramic Fibers
CAS Number: None
Date: July 17, 2002
Profile Status: Draft for Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 70
Species: Fischer 344 Rats

Minimal Risk Level: 0.03 [ ] mg/kg/day [ ] ppm [X] fiber/cc

Reference:

Mast RW, McConnell EE, Anderson R, et al. 1995a. Studies on the chronic toxicity (inhalation) of four types of refractory ceramic fiber in male Fischer 344 rats. Inhal Toxicol 7:425-467.

Mast RW, McConnell EE, Hesterberg TW, et al. 1995b. Multiple-dose chronic inhalation toxicity study of size-separated kaolin refractory ceramic fiber in male Fischer 344 rats. Inhal Toxicol 7(4):469-502.

Experimental design and effects noted:

In the multiple-dose study (Mast et al. 1995b), four groups of about 140 male F344 rats were exposed via nose-only inhalation to 0 (filtered air controls), 3, 9, or 16 mg/m^3 of a refractory ceramic fiber called RCF1, 6 hours/day, 5 days/week for up to 24 months. The companion study (Mast et al. 1995a) exposed two groups of about 140 male F344 rats to 0 or 30 mg/m^3 RCF1 (from the same lot as the multiple-dose study) via the same protocol.

The RCF1 test material was obtained from Carborundum Company, Niagra Falls, New York and was separated (before aerosol generation) to concentrate the numbers of fibers with a targeted nominal arithmetic mean diameter of 1 µm and length of 20–30 µm. These dimensions were chosen based on results of an unpublished simulated workplace exposure study showing airborne fibers to be principally of this size range. The generated aerosols had the characteristics listed in Table A-1. In addition to fibers (i.e., particles with length $\geq$5 µm and length:diameter $\geq$3), the aerosols contained nonfibrous particles, often referred to as "shot". The ratio of fibers to nonfibrous particles in the aerosols ranged from 0.9 to 1.5.

Table A-1. RCF1 Aerosol Characteristics in the 2-Year Inhalation Bioassays with F344 Rats (Mast et al. 1995a, 1995b)

Character [mean (± standard deviation)]	3 mg/m^3	9 mg/m^3	16 mg/m^3	30 mg/m^3
Gravimetric concentration (mg/m^3)	3.0±0.4	8.8 ±0.7	16.5±1.1	29.1±5.2
Total fibers/cc (L$5 µm; L:D$3)	36± 17	91±34	162±37	234±35
WHO fibers/cc (L$5 µm; D<3 µm; L:D$3)	26±12	75±35	120±35	187±53
Diameter (D) range (µm)	0.08-5.32	0.08-5.37	0.07-4.83	0.12-4.53
Length (L) range (µm)	0.77-93.93	1.09-98.25	1.24-97.88	1.30-76.6
Arithmetic mean D (µm)	1.02±0.73	1.02±0.71	1.02±1.70	0.98±0.61
Geometric mean D (µm)	0.80±2.06	0.80±2.03	0.82±1.99	0.82±1.89
Arithmetic mean L (µm)	20.2±18.10	20.3±17.1	19.6±16.5	22.3±17.0
Geometric mean L (µm)	13.5±2.60	13.9±2.50	13.8±2.4	15.9±2.4

Groups of 3–6 rats from each exposure group were killed at 3, 6, 12, 18, and 24 months of exposure. Additional groups of 3–6 rats were removed from exposure at 3, 6, 12, and 18 months and exposed to filtered air until they were sacrificed at 24 months. Remaining rats exposed for 24 months (15–32 rats per group) were held without further exposure until 30 months when survivors were killed. All rats were necropsied. Lung tissues were removed, weighed, and the left lung was prepared for routine histopathology that included staining for collagen deposition. Other tissues processed for histopathology included the nasal cavity, larynx, trachea, bronchi, mediastinal and mesenteric lymph nodes, liver, spleen, kidneys, heart, and all tissues with grossly visible lesions. The concentration and size distributions of fibers in lung tissue were determined after ashing of accessory lung lobes. All fibers detected in lungs had diameters <3 µm. Concentrations were expressed as total fibers per mg dry lung (length:diameter >3) or WHO fibers per mg dry lung (length >5 µm, diameter <3 µm, and length:diameter $3).

Observed nonneoplastic lung lesions were classified with two different grading scales. One scale contained eight grades ranging from a normal grade of 1 (with no lesions observed), through "cellular change" grades 2 and 3 (few to conspicuous macrophages in terminal bronchioles and alveoli and no collagen deposition at the bronchiolo-alveolar junction), to "fibrosis" grades increasing in severity from grade 4 (minimal collagen deposition at the bronchoalveolar junction; increased bronchiolization; and associated mucoid debris) to grade 8 (complete obstruction of most airways). The other scale contained five grades (0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked) and was applied to particular histopathological findings (macrophage aggregation, bronchiolization, granuloma presence, interstitial [i.e., pulmonary] fibrosis, and pleural fibrosis).

Survival was not statistically significantly affected in any of the exposed groups compared with controls. Body weights and body weight gains were not affected in the two lowest exposure groups (3 and 9 mg/m^3). At sporadic intervals of exposure, rats exposed to 16 or 30 mg/m^3 displayed statistically significant decreases in body weight, compared with controls. The decreases were not >10% of control values, and are not considered an adverse effect. As early as 3 months after exposure, absolute and relative lung weights were significantly greater in rats exposed to 16 or 30 mg/m^3. After 24 months of exposure, absolute lung weights were respectively increased by 32 and 65%, compared with controls. The lung weight changes are considered to be an indicator of pulmonary inflammation from repeated exposure to RCF1. Lung fiber concentrations increased with increasing exposure duration and concentration; at 24 months, mean values of WHO fibers/mg lung were 4.29x10^4, 15.60x10^4, 22.10x10^4, and 27.50x10^4 for the 3-,9-, 16-, and 30-mg/m^3 groups, respectively.

Exposure-related nonneoplastic histopathological lesions were restricted to the lung or pleura. Signs of pulmonary inflammation (macrophage aggregation, bronchiolization, and granuloma presence) were observed in all exposed groups after 3 months of exposure, whereas these lesions did not occur in the control rats at any interval (see Table A-2). At 24 months, mean scores (on the five-grade scale) in the 3- and 30-mg/m^3 groups ranged from 2 to 3.2 for macrophage aggregation, from 1.2 to 2.7 for

bronchiolization, and from 1.5 to 2 for granuloma presence (Table A-2). The mean scores reflect progression of the inflammatory lesions with exposure duration and concentration (Table A-2). Distinct signs of pulmonary fibrosis and pleural fibrosis appeared in rats exposed to concentrations $9 mg/m^3 and showed progression in severity with exposure duration and concentrations (Table A-2). Signs of fibrosis did not appear until 12 months of exposure. Using the eight-grade scale to classify the pulmonary cellular changes and fibrosis, the mean scores at 24 months were 1.0 (normal), 3.2, 4.0, 4.2, and 4.0 for the control, 3-, 9-, 16-, and 30-mg/m^3 groups, respectively. In rats exposed for 24 months and allowed to live without exposure to 30 months, respective mean scores were 1.0, 2.9, 3.8, 4.0, and 4.3 (Table A-2). These scores indicate that the pulmonary lesions produced by 24 months of exposure showed only minor, if any, regression and that, on average, the most severe nonneoplastic lesions formed were classified as minimal to mild fibrosis. It was reported that the principal difference between 24-month exposed rats killed at 24 and 30 months was a reduction in the number of pulmonary macrophages and granulomas in the 30-month rats; pulmonary or pleural fibrosis showed no signs of regression.

Neoplastic lesions (lung adenomas, lung carcinomas, and mesotheliomas) were found most prominently in rats exposed to 30 mg/m^3. The tumors appeared predominately late in life. The first adenoma occurred in rats sacrificed at 18 months; carcinomas and mesotheliomas were detected only in the 30-month-sacrifice animals. Incidences for rats (that survived to 12 months) with bronchoalveolar hyperplasia were 8/129, 10/123, 16/127, 13/124, and 17/123 for the control through high-exposure groups. Combined incidences for lung adenomas or carcinoma were 1/129, 2/123, 5/127, 2/124, and 16/123. Incidences for mesothelioma were 0/129, 0/123, 1/127, 0/124, and 2/123. Incidences for mesothelial proliferation were 1/129, 0/123, 1/127, 1/124, and 9/123.

Table A-2. Severity Scores for Pulmonary Lesions in F344 Rats Exposed to RCF1 (Mast et al. 1995a, 1995b)[a,b]

Exposure level/ sacrifice month	Number of rats	Macro-phage (0–4 Scale)	Bronchio-lization (0–4 Scale)	Granuloma (0–4 Scale)	Pulmonary fibrosis (0–4 Scale)	Pleural fibrosis (0–4 Scale)	8-Grade score for pulmonary cellular change and fibrosis
Control							
3	3	0	0	0	0	0	1.0
6	3	0	0	0	0	0	1.0
12	6	0	0	0	0	0.3	1.0
18	6	0	0	0	0	0	1.0
24	6	0	0	0	0	0	1.0
30[b]	32	0.1	0.1	0	0	0	1.0
3 mg/m^3							
3	3	1.7	0	0.7	0	0	2.0
6	3	1.7	0	1	0	0	2.0
12	6	2	1	1.3	0.2	0	3.0
18	6	2	1.2	1.7	0.7	0.7	3.2
24	6	2	1.2	1.5	0.7	0.5	3.2
30[b]	23	2.4	1.7	1.5	0.8	0.5	2.9
9 mg/m^3							
3	3	2	0.3	1.3	0	0	2.3
6	3	2	0.7	2	0	0.3	2.7
12	6	2.3	1.2	2.2	1.7	0.2	4.0
18	6	2.3	1.8	2.2	1.8	0.7	4.0
24	6	2.5	1.8	2.2	2	0	4.0
30[b]	25	2.7	1.7	1.7	1.7	0.5	3.8
16 mg/m^3							
3	3	2	1	2	0	0	3.0
6	3	2.3	1.3	2	0	0	3.0
12	6	3	1.8	2.8	2.8	0.7	4.0
18	6	3	2.7	2.7	2.2	1.2	4.0
24	6	3	2.7	2.7	2.8	1.5	4.2
30[b]	20	3	2.5	2.1	2	1	4.0
30 mg/m^3							
3	3	2	1	2	2	0	3.3
6	3	2.7	2	2	2	0	4.0
12	6	3	2.3	2.5	2.5	1.5	4.0
18	3	3	2	2.3	2.3	1	4.3
24	6	3.2	2.7	2	2	0.5	4.0
30[b]	15	2.8	2.9	1.9	1.9	1.3	4.3

[a]0–4 Scale for different types of lesion: 0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked.
8-Grade Scale for pulmonary cellular change and fibrosis: 1=normal; 2 or 3=cellular change consistent with inflammation; 4–8=increasing severity of fibrosis from minimal to severe.
[b]Exposed for 24 months and sacrificed at 30 months.

Dose and end point used for MRL derivation:

Benchmark concentration analysis was conducted for lung weight (absolute weight expressed as percent of control), macrophage aggregation score, and bronchiolization score. Changes in these variables are taken as signs of pulmonary inflammation induced by refractory ceramic fibers deposited in the lung. ATSDR policy considers pulmonary fibrosis to be a serious adverse effect that is inappropriate for MRL derivation, and therefore, scores for pulmonary or pleural fibrosis were not included in the analysis.

Continuous-variable models available in the EPA Benchmark Dose Software were fit to the lung weight, macrophage, and bronchiolization data shown in Table A-3. Data for group means and standard deviations were obtained from an analysis of the Mast et al. (1995a, 1995b) 24-month-sacrifice data by Dr. C.P. Yu (University of Buffalo, personal communication). The published report by Mast et al. only cited mean values and did not cite standard deviations. Dr. Yu's analysis did not include scores (and standard deviations) for granuloma presence.

The benchmark response level for lung weight was set arbitrarily at 10% change in weight; percentage change below this value is assumed to be nonadverse. Benchmark response levels for scores for macrophage aggregation and bronchiolization were set at 1.0 (minimal rating on the 0–4 scale, where 0=normal).

For the benchmark concentration analysis, rat exposure levels were converted to human equivalent exposure levels (shown in Table A-3) using rat and human lung deposition and clearance models for RCF1 developed by Dr. C.P. Yu and colleagues (Yu et al. 1995a, 1995b, 1996, 1997, 1998a, 1998b). The equations for deposition are functions of fiber length, fiber diameter, and time. The equations for mechanical macrophage-mediated clearance rate are functions of fiber length, alveolar macrophage volume, and lung burden (total accumulated volume of fibers and particles). The clearance models include dissolution-rate and transverse breakage-rate equations. The calculations were made by Dr. Yu (personal communication). Retained total *fiber surface area* per area of pulmonary surface was the dose metric used in these calculations, although human equivalent concentrations based on retained total fiber number per area of pulmonary surface resulted in very similar values. Human equivalent exposure concentrations of 0, 2.0, 7.0, 8.8, and 12.3 fiber/cc were calculated from the empirical rat exposure levels of 0, 36, 91, 162, and 234 total fibers/cc, respectively (Table A-3; see key assumptions in next paragraph). Human equivalent exposure concentrations based on retained total *fiber number* per area of pulmonary surface were 0, 2.1, 6.8, 9.3, or 11.8 fiber/cc.

Key assumptions made in the dosimetric calculations included the following:

Rat lung surface area: 4.3×10^3 cm^2; Human lung surface area: 6.5×10^5 cm^2
Rat macrophage volume per lung: 26 mm^3; Human macrophage volume per lung: 1.75×10^4 mm^3
Rat macrophage diameter: 10.68 µm; Human macrophage diameter: 16.82 µm
Dissolution rate (same in rats and humans): 6.46×10^{-5} (µm/day)
Breakage rate and scheme: same in rats and humans
Continuous exposure of humans: 24 hours/day, 7 days/week, 52 weeks/year, 70 years
Continuous human (nose) breathing at rest (750 mL tidal volume; 14.5 $minute^{-1}$ breathing rate)
Size distribution of refractory ceramic fibers in the human model:
    Bivariate lognormal distribution (geometric mean±standard deviation) similar to workplace RCF size data: fiber diameter: 0.84 µm (±2.05); fiber length: 14.1 µm (±2.48)
Rat model: retained volume of nonfibrous plus fibrous particles (lung burden) impacts clearance rate
Human model: only retained fibrous particle volume impacts clearance rate

Table A-3. Non-neoplastic Lung Responses in F344 Rats Exposed for 24 Months to RCF1 by Inhalation (Mast et al. 1995a, 1995b) and Human Equivalent Exposure Concentrations (HEC) Calculated with Models for RCF1 Developed by Yu et al. (1995a, 1996, 1997, 1998)

Exposure level (total fibers/cc)		Lung weight	Macrophage aggregation	Bronchiolization	Pulmonary fibrosis
Rat	HEC	(Percent of control)	Mean score±standard deviation (0–4 Scale)		
0	0	100.0±14.0	0±0	0±0	0±0
36	2.0	116.8±12.3	2.0±0	1.2±0.4	0.7±0.8
91	7.0	110.9±8.1	2.5±0.6	1.8±0.4	2.0±0
162	8.8	131.8±15.3	3.0±0	2.7±0.5	2.8±0.4
234	12.3	164.7±44.2	3.2±0.4	2.7±0.5	2.2±0.4
0–4 Scale: 0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked					

[ ] NOAEL [ ] LOAEL [X] Benchmark Concentration: Lower 95% confidence limits on benchmark concentrations (lower confidence limit on the estimated human equivalent concentration associated with a mean score of 1.0 for macrophage aggregation or bronchiolization or 10% increase in lung weight) were considered as the basis of the MRL.

Benchmark Modeling Results. Available continuous-variable models in the EPA Benchmark Dose Software (linear, polynomial, power, and Hill models) were fit to the data shown in Table A-3.

Lung Weight. Adequate fits to the data (as assessed with a chi-square goodness of fit test with a rejection criteria of Chi-square probability <0.05) were obtained with the polynomial, power, and Hill models with constant variance assumed. Statistical tests indicated that variances were not constant across exposure groups (this is reflected in the standard deviations listed in Table A-3), but models with non-homogeneous variance (i.e., variance as a power function of dose) provided poor fits to the data. Predicted human equivalent benchmark concentrations (i.e., predicted concentrations associated with 10% increase in lung weight, and their lower 95% confidence limits in parentheses) from the power, polynomial, and Hill models (with constant variance) were similar: 6.0 (2.7) fibers/cc; 6.7 (3.6) fibers/cc; and 7.1 (5.1) fibers/cc, respectively. Using 15% increase in lung weight as the benchmark criterion, respective benchmark concentrations from these models were only slightly higher: 7.7 (4.8) fibers/cc; 7.1 (3.8) fibers/cc; and 8.1 (5.3) fibers/cc.

Macrophage Aggregation Scores. Statistical tests of fit indicated inadequate fit of the data by each of the available models with constant variance. Models with variance as a power function of dose did not improve the fits to the data. Predicted human equivalent benchmark concentrations (concentrations associated with a mean score of 1.0, and their lower 95% confidence limits) from the linear, polynomial, power, and Hill models (constant variance) were: 2.0 (1.1) fibers/cc; 1.5 (1.1) fibers/cc; 2.0 (1.1) fibers/cc; and 0.6 (0.5) fiber/cc.

Bronchiolization Scores. Statistical tests of fit indicated inadequate fit of the data by each of the available models with constant variance. Models with variance as a power function of dose did not improve fit to the data. Predicted human equivalent benchmark concentrations (concentrations associated with a mean score of 1.0, and their lower 95% confidence limits) from the linear, polynomial, power, and Hill models (constant variance) were: 3.3 (2.6) fibers/cc; 2.4 (2.0) fibers/cc; 3.3 (2.6) fibers/cc; and 1.8 (1.3) fibers/cc.

Selection of MRL Basis. Macrophage aggregation score is selected as the basis of the chronic inhalation MRL, since it appears to be the most sensitive pulmonary inflammation indicator among the three

considered from the Mast et al. (1995a, 1995b) data. The statistical inadequacy of the fits of the models to the lesion score data is likely influenced strongly by the small number of rats in each exposure group (n=6, except for the control where n=12). Visual examination of the predicted and observed lesion scores, however, shows a reasonable agreement (for examples, see Figures A-1 and A-2 showing observed and predicted scores for macrophage aggregation and bronchiolization from the polynomial models). Because of this agreement, it appears reasonable to use the models to select the point of departure for MRL derivation.

The benchmark concentration analysis of the macrophage aggregation scores predicted human equivalent concentrations ranging from 0.6 to 2.0 fiber/cc (depending on model) that were associated with a "minimal" score for macrophage aggregation (mean score of 1 on the 0–4 scale). The lower 95% confidence limits on these concentrations ranged from 0.5 to 1.1 fiber/cc. An approximate median value of 1 fiber/cc from this range is selected as the point of departure to which uncertainty factors (noted below) are applied to derive the MRL.

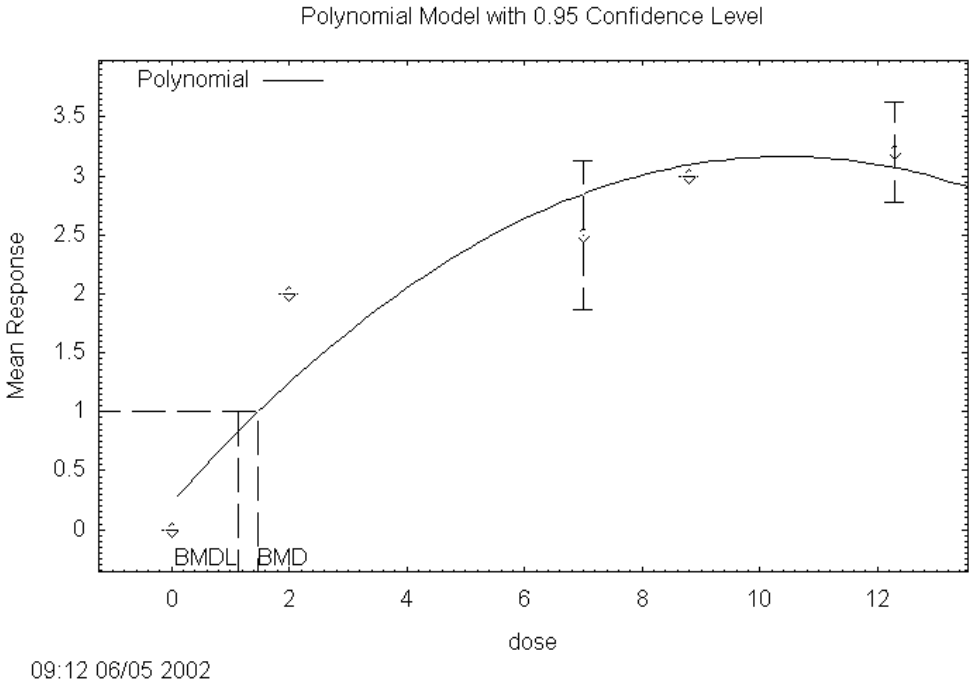


Figure A-1. Predicted (line) and observed (diamonds) mean scores for macrophage aggregation (0–4 scale) plotted against human equivalent concentrations of RCF1 ("dose" = total fibers/cc). BMD refers to the benchmark concentration associated with a score of 1. BMDL is the 95% confidence lower limit on the benchmark concentration.

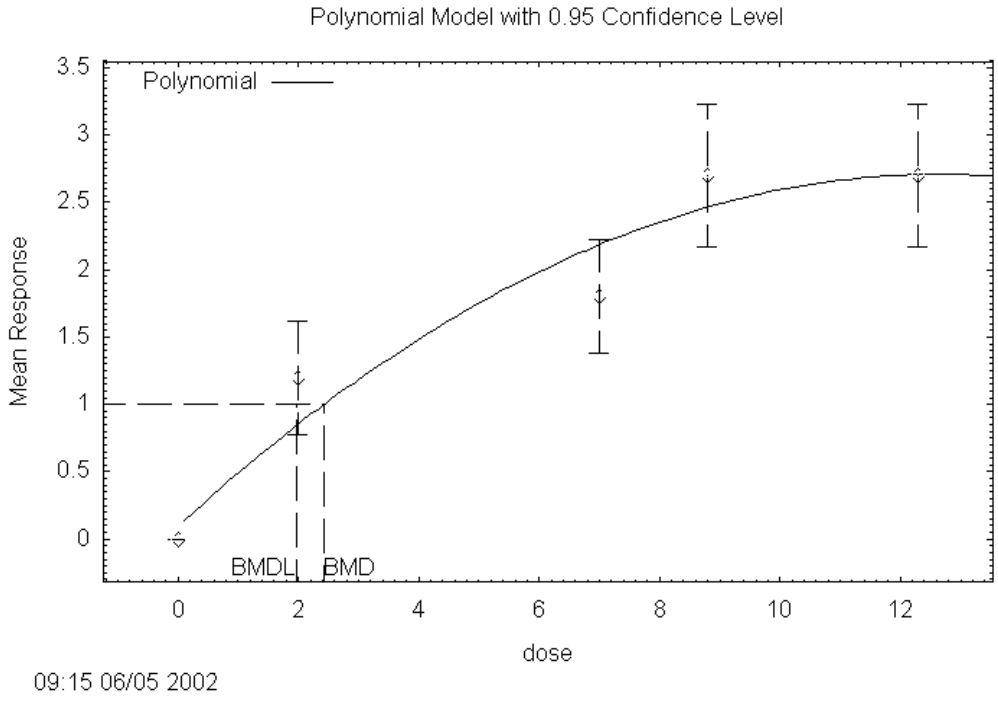


Figure A-2. Predicted (line) and observed (diamonds) mean scores for bronchiolization (0–4 scale) plotted against human equivalent concentrations of RCF ("dose" = total fibers/cc). BMD refers to the benchmark concentration associated with a score of 1. BMDL is the 95% confidence lower limit on the benchmark concentration.

Uncertainty Factors used in MRL derivation:

[X] 3 for interspecies extrapolation with dosimetric adjustment: The dosimetric adjustment takes into account physiological differences between rats and humans expected to influence deposition and clearance of refractory ceramic fibers from the lung. The derivation assumes that rats and humans are equally responsive to retained fibers in the lung, in the absence of conclusive evidence to indicate otherwise. The uncertainty factor of 3 accounts for the uncertainty associated with this assumption of interspecies pharmacodynamic equivalence.

[ ] 10 for use of a LOAEL: No uncertainty factor for the use of a LOAEL is applied. Benchmark concentration analysis predicted surrogate NOAELs for lung weight (95% lower confidence limit on concentration associated with 10% increase in lung weight) and scores for macrophage aggregation and bronchiolization (95% lower confidence limits on concentrations associated with average minimal scores for these lesions).

[X] 10 for human variability

Chronic inhalation MRL=1 fiber/cc÷(3x10)=0.03 fiber/cc

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

Was a conversion used from intermittent to continuous exposure? Yes.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: See previous discussion of the calculations made with the rat and human lung deposition and clearance

models for RCF1 developed by Dr. C.P. Yu and colleagues (Yu et al. 1995a, 1995b, 1996, 1997, 1998a, 1998b).

Other additional studies or pertinent information that lend support to this MRL:

The Mast et al. (1995a, 1995b) study provides the best available data describing dose-response relationships for nonneoplastic lesions in the lung and pleura from chronic inhalation exposure to refractory ceramic fibers. The study identifies pulmonary inflammation as the critical nonneoplastic endpoint of concern and identifies other more serious effects at higher exposure levels (pulmonary and pleural fibrosis and cancer of the lung and pleura). Other studies of rats exposed to RCF1 by inhalation provide strong support for pulmonary inflammation as the critical end point (Bellman et al. 2001; Everitt et al. 1997; Gelzleichter et al. 1999; McConnell et al. 1995), as well as other animal inhalation studies of other refractory ceramic fibers (Mast et al. 1995a) and other synthetic vitreous fibers such as insulation glass wools, MMVF10 and MMVF11 (Hesterberg et al.1993c; McConnell et al. 1999), slag wool MMVF22 (McConnell et al. 1994), and rock wool MMVF21 (McConnell et al. 1994).

There are distinct differences between laboratory animal species and humans in respiratory tract size and geometry, ventilation rate and pattern, and macrophage sizes that influence the retention (the net result of deposition and clearance) of fibers in the lung. Yu and colleagues (Yu et al. 1995a, 1995b, 1996, 1997, 1998a, 1998b) have developed lung retention models for RCF1 in rats and humans that incorporate many of these interspecies differences. These models significantly decrease uncertainty in extrapolating doses from rats to humans.

The MRL derivation assumes that rats and humans are equally sensitive to the inflammatory effects of refractory ceramic fibers. In contrast to the relatively robust understanding of pharmacokinetics of fibers in animals and humans, understanding of the relative sensitivity of rodents and humans to synthetic vitreous fibers or asbestos fibers (i.e., the relative pharmacodynamics) is poor. Varying opinions on the relative sensitivity of rodents and humans to deposited fibers have been expressed by Rodelsperger and Woitowitz (1995), Rowe and Springer (1986), and Maxim and McConnell (2001). The uncertainty factor of 3 is used in the MRL derivation to account for the uncertainty of the assumption of pharmacodynamic equivalence between rats and humans.

Available comparative data with other refractory ceramic fibers (e.g., data for RCF2, RCF3, and RCF4 reported by Mast et al. 1995a) suggest that RCF1 is as potent or more potent than other refractory ceramic fibers. Thus, the chronic MRL based on RCF1 data is expected to be protective of the public health for exposure to other refractory ceramic fibers. In addition to its relatively high durability, a contributing factor to the high potency of RCF1 relative to other refractory ceramic fibers is the high content of nonfibrous particles in RCF1. Bellmann et al. (2001) have reported that the mass concentration of total fibers (particles with aspect ratio >3:1) and nonfibrous particles (with aspect ratios <3:1) in RCF1 are 0.76 and 0.26 ng/ng RCF1, respectively. Some evidence that the presence of the nonfibrous particles can enhance the effects on the lung was provided by comparing responses in rats exposed by inhalation for 3 weeks to concentrations of about 125 fibers (with lengths >20 μm)/cc of either RCF1 or a sample of refractory ceramic fibers, called RCF1a, in which only 2% of the mass was accounted for by nonfibrous particles (Bellmann et al. 2001). Expressed as WHO fibers/cc, the respective mean concentrations were 481 fibers/cc for RCF1a and 679 fibers/cc for RCF1. Pulmonary clearance ability was markedly depressed by RCF1, but not by RCF1a, and indices of pulmonary inflammation were more persistently increased by RCF1 than by RCF1a (Bellmann et al. 2001).

The chronic MRL is also expected to be appropriately applied to intermediate-duration exposure scenarios, based on evidence from interim sacrifice data from the Mast et al. (1995b) bioassay that exposure-response relationships for pulmonary inflammation and chronic exposure are similar to those for intermediate-duration exposure. Scores for pulmonary inflammation progressed to only a limited degree

with progression from intermediate to chronic duration. For example, mean scores for macrophage aggregation in rats exposed to 3, 9, 16, and 30 mg/m^3 at 3 months were 1.7, 2, 2, and 2, respectively. At 12 and 24 months, the respective scores were: 2, 2.3, 3, and 3; and 2, 2.5, 3, and 3.2.

Dose-response relationships for pulmonary inflammation from acute inhalation exposure to synthetic vitreous fibers are inadequately characterized for deriving an acute inhalation MRL for any type of synthetic vitreous fiber.

Any use of the MRL for refractory ceramic fibers in assessing health hazards from the insulation wools should acknowledge the evidence that many of the insulation wools are markedly less durable and less potent than refractory ceramic fibers (Bernstein et al. 2001a, 2001b; Eastes and Hadley 1996; Eastes et al. 2000; Hesterberg et al. 1998a). There are data from multiple-exposure-level 2-year rat inhalation bioassays on the glass wools, MMVF10 and MMVF11 (Hesterberg et al.1993c; McConnell et al. 1999), the slag wool MMVF22 (McConnell et al. 1994), and the rock wool MMVF21 (McConnell et al. 1994) that adequately describe dose-response relationships for nonneoplastic pulmonary effects from intermediate- and chronic-duration exposure to these materials. However, lung retention models for these synthetic vitreous fibers are not yet fully developed to carry out physiologically based dosimetric calculations of human equivalent concentrations. When these models are available, they could be used to convert rat exposure concentrations to human equivalent concentrations, and use the data for MMVF10, MMVF11, MMVF22, and MMVF21 to derive inhalation MRLs for insulation wools.

There are no adequate data (from multiple-exposure level studies) for deriving inhalation MRLs for the other types of synthetic vitreous fibers (special applications glass fibers or continuous filament glass fibers that are woven).

Agency Contact (Chemical Manager): Malcolm Williams, D.V.M., Ph.D.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These

MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory

effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

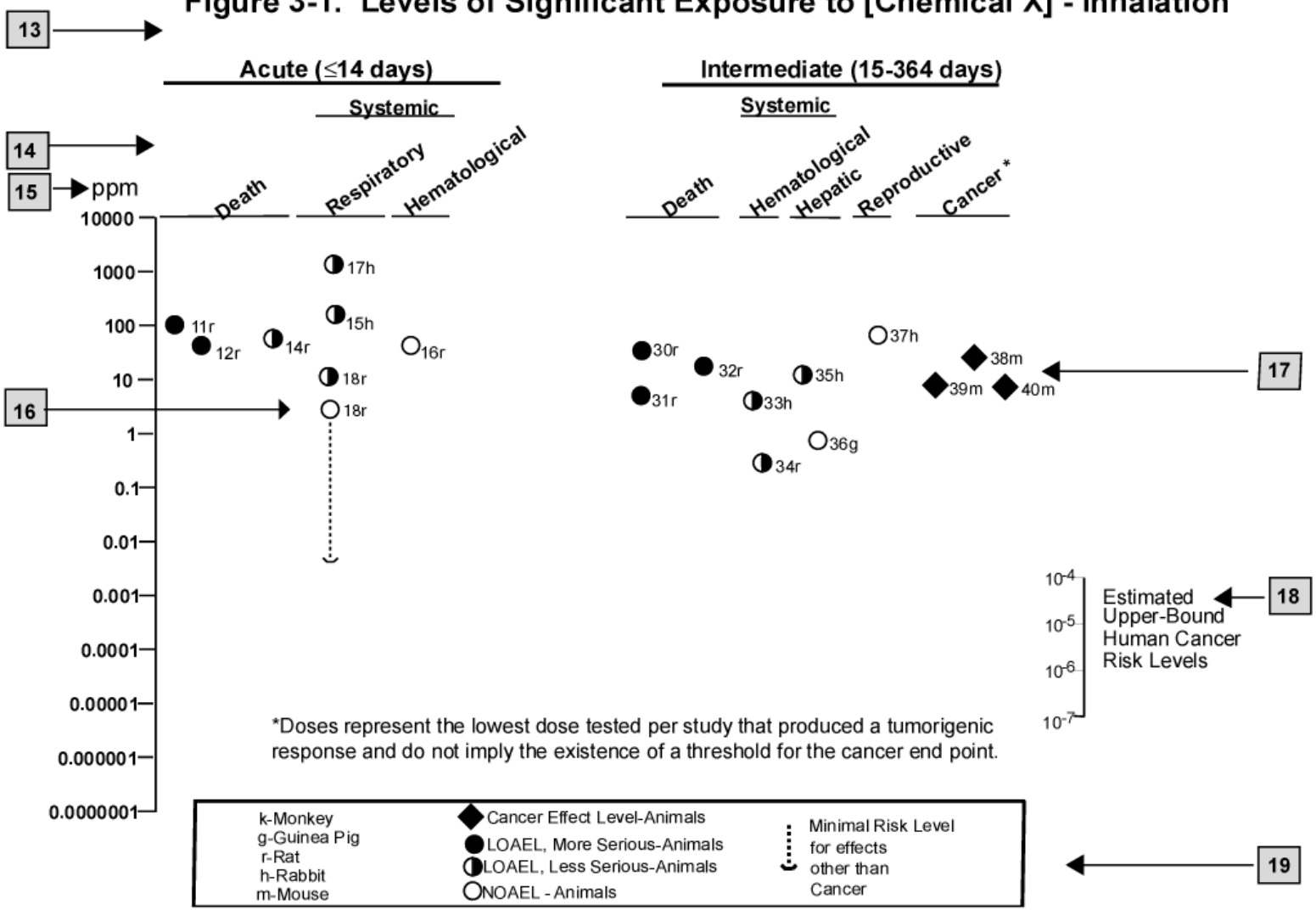
Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
Systemic	9	9	9	9	9		9
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					9		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 3-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotranferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

APPENDIX C

DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	*Federal Register*
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic

PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
$	greater than or equal to

=	equal to
<	less than
#	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D

INDEX